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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/757,298	01/14/2004	Robert S. Andrews	CHEM0001US	5625

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EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/757,298	ANDREWS ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 September 2005 and 25 May 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6-15 and 20-41* is/are pending in the application.

4a) Of the above claim(s) *6,7,20-37,39 and 40* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,8-15,38 and 41* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Status of the application

Claims 1, 6-15 and 20-41 are pending. Claims 6, 7, 20-37, 39 and 40 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention or a non-elected species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on July 8, 2005.

Claims 1, 8-15, 38 and 41 are examined on the merits.

Response to arguments: Claim Rejections - 35 USC § 103

Claims 1 and 13 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Iyer et al. in view of Tosquellas et al. for the reasons set forth in the office action mailed on September 23, 2005.

Applicant traverses the rejection over Iyer et al. in view of Tosquellas et al. by stating that the only data Iyer provides is directed to the enzyme stability of oligonucleotides having small lipophilic groups that have been treated with serum esterases. Applicant argues that because most lipophilic conjugates known in the art are larger groups, the invention taught by Iyer is actually a linkage attaching a lipid group to an oligonucleotide. Applicant argues that each example taught by Iyer has

only one methylene group and not the two consecutive methylene groups present in the SATE group in the instant claims. These arguments regarding the teachings of Iyer are not persuasive because while applicant is correct that the exemplified embodiments of Iyer have only one methylene group, the disclosure is not limited to the exemplified embodiments. Iyer et al. teach on pages 19-22 that lipophilic groups can be attached to oligonucleotides by any known protocol; therefore groups having two consecutive methylenes are not excluded from the teachings of the reference. Also, regardless of applicant's conclusion, Iyer et al. teach their invention is compositions and methods of increasing cellular uptake by use of oligonucleotide prodrugs (see pages 5-8) and not merely a linkage for attaching lipid groups as alleged by applicant.

Applicant argues that the use of the SATE group in the invention of Iyer would render lipid substitution impossible because SATE groups are not taught as variable linker groups having lipid groups attached thereto. This argument is not persuasive because Iyer actually teaches the attachment of lipophilic groups, not just lipids. Iyer et al. define these groups on page 19 as including alkyl groups and because SATE includes an alkyl group, it falls within the definition of lipophilic provided by Iyer et al.

Applicant further argues that Tosquellas et al. teaches away from the combination with Iyer et al. because a definitive conclusion regarding the bioavailability of modified oligonucleotides comprising SATE groups has not been reached. Applicant appears to be arguing that there would be no reasonable expectation of success in combining the teachings of Iyer and Tosquellas. However, a finding of obviousness does not require that all possible problems have been resolved, only that there is a reasonable expectation of success. The statements of Tosquellas et al. merely indicate

some data is lacking, not that SATE groups do not work. Based on the *in vitro* data taught in the reference that SATE groups are removed by cellular enzymes and the *in vivo* data cited on page 2069, column 2, one of ordinary skill in the art would have a reasonable expectation of success in making oligonucleotides comprising a SATE group at a 5' phosphate.

Applicant's arguments regarding the 103 rejections over Boutla in view of Iyer and further in view of Parrish are moot because those rejections have been withdrawn in favor of the following new rejections.

New Claim Rejections - 35 USC § 103

Claims 1, 8-13, 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable Boutla et al. (of record) in view of Tosquellas et al. (of record).

The claims are directed to oligomeric compounds comprising a plurality of 2'-hydroxyl ribonucleotides and a phosphate at the 5' terminus comprising a SATE protecting group. In specific embodiments, the oligomeric compound may have the structure shown in claim 13 and may be double stranded, one strand may be an antisense strand and a protected phosphate may be on one or both of the two strands.

Boutla et al. teach (see the abstract) that siRNAs that are phosphorylated at the 5' end are more active than siRNAs having 5' hydroxyl ends. Boutla et al. do not teach siRNAs having protected phosphate groups.

Tosquellas et al. teach that the effectiveness of oligonucleotide-based therapy has been limited due to problems such as serum instability and adverse

pharmacokinetics. Tosquellas et al. hypothesize that the anionic charge of oligonucleotides contributes to the problems with oligonucleotides (see introduction, page 2069). To overcome the shortcomings of natural phosphodiester linkages, Tosquellas et al. suggest using a prodrug approach, and teach the synthesis of pro-oligonucleotides using nucleotide synthons having SATE protecting groups on the internucleotide phosphorus atoms. This protecting group has been known to be enzymolabile for mononucleotides both *in vitro* and *in vivo* (see second column of page 2069). Tosquellas et al. teach that SATE is removed from pro-oligonucleotides by esterases in cell extracts to provide a natural phosphodiester linkage.

It would have been obvious to one of ordinary skill in the art to make the siRNAs having a 5' phosphate taught by Boutla et al. as an oligonucleotide comprising SATE as taught by Tosquellas et al. Boutla et al. provide a motivation to make siRNAs with a phosphate at the 5' end by teaching that such siRNAs are more reactive than those having a 5' hydroxyl group while Tosquellas et al. provide a motivation to make a pro-oligonucleotide comprising SATE by teaching that this group is removed by cellular esterases. One of ordinary skill in the art would have had a reasonable expectation of success in making an siRNA having SATE protected phosphorus at the 5' end because Tosquellas et al. teach synthons comprising SATE and their use to synthesize oligonucleotide prodrugs.

Thus, the invention of claims 1, 8-13, 38 and 41 would have been obvious, as a whole, at the time of invention.

Claims 1, 8-15, 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Boutla et al. and Tosquellas et al. as applied to claims 1, 8-13, 18 and 38 above, and further in view of Parrish et al. (of record).

Claims 1, 8-13, 38 and 41 are described in the previous 103 rejection. Claims 14 and 15 limit claim 13 by stating the oligomeric compound of claim 13 has at least one T_3 position as fluorine (F) optionally with additional T_3 position as a sugar substituent.

The teachings of Boutla et al. and Tosquellas et al. are described in the previous 103 rejection. These references do not teach sugar substituents that include fluorine.

Parrish et al. teach the functional anatomy of the dsRNA active in RNA interference. Parrish et al. teach that dsRNAs with substitutions routinely used in the art of antisense for providing desirable characteristics such as increased nuclease stability, including 2'-fluoro and 2-OMe substitutions, are tolerated in RNA interference (see figure 5).

The teachings of Boutla et al. and Tosquellas et al. are obvious for the reasons given in the previous 103 rejection. It would have been further obvious to make siRNAs having a protected 5' phosphate group and sugar substituents because Parrish et al. teach that sugar substituents well-known in the art of antisense for providing nuclease stability are tolerated in RNA interference. One of ordinary skill in the art would have had a reasonable expectation of success in making siRNAs having 2'-fluoro or other sugar substitutions because Parrish et al. teach that double stranded RNAs having this substituent function in RNA interference.

Thus, the invention of claims 1, 8-15, 38 and 41 would have been obvious, as a whole, at the time of invention.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
August 4, 2006

JANE ZARA, PH.D.
PRIMARY EXAMINER

TC1600